UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,076	07/07/2003	Steven M. Ruben	PZ034P1C2	8540

22195 7590 01/25/2007

HUMAN GENOME SCIENCES INC.
INTELLECTUAL PROPERTY DEPT.
14200 SHADY GROVE ROAD
ROCKVILLE, MD 20850

EXAMINER	
DANG, IAN D	
ART UNIT	**PAPER NUMBER**
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,076	RUBEN ET AL.	
	Examiner	Art Unit	
	Ian Dang	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,30-38 and 48* is/are pending in the application.

4a) Of the above claim(s) *48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25, 30-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *25,30-38 and 48* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/18/2006 has been entered.

This Office Action is in response to the amendment and response filed on 12/18/2006. Claims 1-24, 26-29, 39-47 have been cancelled and claim 48 has been withdrawn. Applicants have amended claim 25. Claims 25 and 30-38 are pending and under examination.

Rejection Withdrawn

35 U.S.C. § 112 (Written Description)

The rejection of claims 25, 27-38 under 35 USC 112, First paragraph is withdrawn in view of the amendment made to claim 25. Applicant's amendments, see at pages 7 and 8, filed on 12/18/2006, with respect to claims 25, and 27-38 have been fully considered and are persuasive.

Rejections maintained

Claim Rejections - 35 USC § 101/112

Claims 25 and 30-38 are rejected under 35 U.S.C. § 101 & § 112, First paragraph for lacking a patentable utility. The basis for this rejection is set forth for claims 25 and 30-38 at pages 2-4 of the previous Office action of 9/21/2006.

The rejections of claims 25 and 30-38 under 35 U.S.C. § 101 & § 112, First paragraph is maintained. Applicant's arguments filed 12/18/2006 have been fully considered but they are not persuasive.

(i) Applicants assert that they have presented reasoning asserting a utility, and the Examiner must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the Applicants' assertion of utility. Applicant argues that the Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101. Applicants allege that the Examiner continues to discount the asserted utilities of HFXHC41 as not credible, contending that there is not proof that HFXHC41 exhibits the biological functions that have been asserted. Applicants alleges that the Examiner is applying the wrong standard that there is not proof that HFXHC41 exhibits the biological functions that have been asserted. It is noted that at pages 4-5 of the Response mailed on 12/18/2006, Applicants cites numerous case laws dealing with utility.

In summary, Applicant's arguments have been fully considered but are not found to be persuasive. The truth, or credibility, of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not specific or substantial. The Examiner acknowledges that "[in] most cases, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. 101 (MPEP § 2107.02 (section III)). However, in the previous Office Actions of 03 April 2006 and 21 September 2006, the Examiner made a *prima facie* showing that the claimed invention lacks utility and provided sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. Essentially, Applicant has not provided evidence to demonstrate that the claimed HFXHC41 polypeptide of the instant application is supported by a specific and substantial

asserted utility or a well-established utility. The Examiner has fully considered all evidence of record and has responded to each substantive element of Applicant's response (see below). It is noted to Applicant that MPEP § 2107.02 (part VI) also states that "only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained".

(ii) Applicant asserts that the specification teaches that HFXHC41 is "expressed primarily in adult brain, multiple sclerosis, human manic depression tissue, spinal cord, hippocampus, subtantia nigra, frontal cortex, and to a lesser extend, in placental." See page 16, paragraph [0045]. The specification teaches that "elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival." See page 17, paragraph [0048]. Accordingly, the specification teaches that the compositions of the claimed invention "are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions." More specifically, the specification states, "the uses include, but are not limited to the detection, treatment, and/or prevention of . . . schizophrenia." Seepages 17-18, paragraph [0048]. It was well known at the time of filing that HA and HA-binding proteins are important in forming the extracellular matrix of the brain and the extracellular matrix is neurotrophic and affects neurite outgrowth. See, Exhibit A.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant's assertion that the claimed HFXHC41 polypeptide is associated with tropic activities is not specific or substantial. Exhibit A of the response mailed 12/18/2006 purports to correlate the function of HFXHC41 to the function of brain extracellular matrix, which has possible trophic

effects on neuronal cells and neurite outgrowth. However, such activities can be performed with any polypeptides and Exhibit A does not refer to the claimed HFXHC41 polypeptide. Applicant has not specifically addressed how this evidence can be specifically be applied to the protein HFCXHC41 claimed in the instant application. Although the specification teaches that the HFXHC41 polypeptide is expressed in normal neuronal cells, Applicant has not provided evidence that the polypeptide HFCXHC41 has any trophic activities. The presence of the polypeptide in neuronal cells is not sufficient to establish that its biological activity is similar to a trophic activity. One of ordinary skill in the art at the time the invention was made would not have been able to use the information obtained from this reference in a useful manner. Therefore, due to little or no guidance in the specification, the skilled artisan would not conclude that HFCXHC41 is associated with a trophic activity.

It is also noted that the HFXHC41 polypeptide of the instant application shares a similarity with the proposed homologs (34% similarity with CD44 and 45% with cartilage linked protein, see Office action mailed 04/03/2006 at page 5) and that the HFXHC41 protein have been demonstrated to be involved in HA binding and tissue distribution. However, function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Bork (1998) teaches that prediction of function from sequence is considerably more complex enterprise that a simple sequence database search (page 721, column 2, 2nd paragraph). In addition, the two link domains of HFXHC41 is not well understood.

The assertion that the disclosed HFXHC41 polypeptide has biological activities similar to other proteins, such as BRAL1 or HAPLN2, and other proteins cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF

(a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF, which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is

considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, one skilled in the art would not know the utility and function of the HFXHC41 polypeptide even if it was a putative trophic factor expressed neuronal cells because neither the prior art nor the specification provides for the physiological significance of the disclosed polypeptide or the purported protein homologs.

(iii) Applicant argues that the burden is on the Examiner to provide evidence to show that the asserted utilities would be considered false. Applicant asserts that the specification teaches that HFXHC41 contains two link domains, is expressed in numerous tissues, is involved in

numerous biological functions, can be used for detection of treatment of schizophrenia and to treat any neurodegenerative disease states, behavioral disorders, on inflammatory conditions. In view of these disclosures, Applicant asserts that a person of ordinary skill in the art would not have doubted the asserted utilities of HFXHC41 at the time the specification was filed.

Applicant's arguments have been fully considered but are not found to be persuasive. The utilities asserted by Applicant are not false but are not specific or substantial and provide insufficient evidence to support that HFXHC41 has utility in the treatment of schizophrenia. Arguments in the absence of evidence are not persuasive.

Furthermore, the specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polypeptide. In order for a polypeptide to be useful, as asserted, for diagnosis/prognosis/prevention of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polypeptide and a disease or disorder. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. Many polypeptides are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polypeptides are either present only in diseased tissue to the exclusion of normal tissue or are expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polypeptide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polypeptides and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself.

Therefore, one skilled in the art would not know the utility and function of the HFXHC41 polypeptide even if it was a putative trophic factor expressed neuronal cells because neither the prior art nor the specification provides for the physiological significance of the disclosed polypeptide or the purported protein homologs.

(iv) In addition, Applicants asserts that Nomoto et al. conclude that the highly informative CA-repeat marker HNCA2 would facilitate the investigation of the possibility that BRAL1 and BCAN genes may be involved in inherited schizophrenia providing evidence utilities to the claimed invention.

Applicant's argument has been fully considered but it is not found to be persuasive. Although Nomoto can facilitate the investigation the BRAL1 and BCAN genes may be involved in Schizophrenia, there is no further evidence to support that HFXHC41 can have any role in Schizophrenia. This relevant literature indicates that the biological functions BRAL1 and BCAN genes are not well understood and require further experimentation.

Therefore, the functions and regulations of the HFXHC41 polypeptide of the instant application, are not well characterized and one skilled in the art the art would not find the utility of HFXHC41 polypeptide to be obvious.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and

art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang
Art Unit 1647
Patent Examiner
January 22, 2007

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER